expressing a botulinum toxin from a prokaryotic expression vector comprising a botulinum toxin nucleotide sequence in a prokaryotic host cell wherein the prokaryotic expression vector includes a weak promoter relative to an unrepressed T7 promoter thereby making a soluble botulinum toxin.

cont'd

132. (amended) The method of claim 126 wherein the botulinum toxin nucleotide sequence specifically hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:27.

REMARKS

The Examiner has imposed a Restriction Requirement for the presently pending claims under 35 U.S.C. 121 dividing the claims into the following Groups.

I. Claim 80 drawn to a soluble fusion protein comprising a portion of Clostridium botulinum toxin A;

II. Claims 113 to 115, 117 to 119 and 122-125, drawn to a method for producing a botulinum toxin by using a weak promoter that is not T7;

III. Claims 116 and 134, drawn to a method for producing a botulinum toxin using T7 promoter;

IV. Claims 113, 120-121 and 122-125, drawn to a method for producing a botulinum toxin by using T71ac promoter; and

V. Claims 126-133, drawn to a method for producing a soluble

botulinum toxin by using a chaperon protein expressed in a host cell.

Claim 80, the sole claim in group I, was canceled in the response to the Office Action dated September 13, 2001. Of remaining groups II, III, IV and V, applicant elects Group II as set forth in claims 113 to 115, 117 to 119 and 122 to 125 with traverse.

Each of pending claims 113 to 134 relate to methods for producing recombinant botulinum toxins using prokaryotic expression systems. Each of the present claims is thus closely related such that a search of one group of claims would necessarily include or encompass a search for the other three groups of claims. In support of this, the Examiner indicates that claims 113 and 122 to 125 are included in both Group II and Group IV.

In view of the above, applicant requests that the restriction requirement be reconsidered and withdrawn.

The Examiner requires applicant to elect a species of botulinum toxin serotype under 35 U.S.C. 121. Applicant elects claims relating to botulinum toxin serotype type A with traverse.

Since all botulinum toxins are believed to operate by a similar mechanism of action, the search performed for botulinum toxin type A should suffice for all of the botulinum toxin serotypes. For example, it is well known that "The botulinum toxins comprise a family of pharmacologically similar toxins that block acetylcholine release from peripheral nerves and cause flaccid paralysis. All of the serotypes of the toxin can poison humans and other animals...", Page 81, left hand side of Schantz, E.J., et al, *Properties and use of Botulinum Toxin and Other Microbial Neurotoxins in Medicine,* Microbiol Rev., 56;80-99:1992

(copy provided). Each of serotypes A, B, C, D, E, F and G are thus closely related such that a search of one botulinum toxin serotype would necessarily include or encompass a search of the other botulinum toxin serotypes.

Therefore, applicant requests that the botulinum toxin serotype species election requirement be reconsidered and withdrawn.

The Examiner requires applicant to elect a species of sequence used for hybridization under 35 U.S.C. 121. Applicant elects claims relating to the nucleotide sequence of SEQ ID NO: 27 with traverse.

Comparative alignment of amino acid sequences of botulinum toxin types A, B, C, D, E, F and G shows multiple, highly conserved domains, Minton, *Molecular genetics of Clostridial Neurotoxins*, Curr. Top. Microbio. Immunol., 195;161 to 194:1995, pages 164 to 173 (copy provided). Each of SEQ ID NO:27, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:65, SEQ ID NO:70 and SEQ ID NO:76 is thus closely related such that it would not impose an undue burden on the Examiner to search each of the sequence listings opposed to a single sequence listing.

Thus, applicant requests that the election of species of sequence requirement be reconsidered and withdrawn.

The present claims 113 to 122, 124, 126 to 130, 132 and 134 read on the elected species and the elected SEQ ID NO.

The Examiner has excluded claims 116, 120 and 121 from Group II stating that Group II claims are drawn to "a method for producing a botulinum toxin by using a weak promoter <u>that is not</u> a T7". Independent claim 113 in Group II is actually drawn to a method for producing a botulinum toxin using promoter that is <u>weak</u>

relative to a T7 promoter. Applicant has amended claim 113 to clarify that the prokaryotic expression vector comprising a botulinum toxin nucleotide sequence includes a promoter that is weak relative to an unrepressed T7 promoter. Applicant submits that the subject matter of claim 116, which specifies a T7 promoter in which expression is repressed, is related to the Group II invention in accordance with amended claim 113.

Claim 120 relates to a T7lac promoter. A T7lac promoter is a T7 promoter which includes a lac operator sequence immediately downstream of the T7 promoter. The lac operator can provide for a reduced or repressed level of transcription by T7 RNA polymerase. Therefore, since a lacT7 promoter can provide weak transcription relative to an unrepressed T7 promoter, applicant submits that the subject matter of claim 120 is within the scope of the Group II invention.

Claim 121 relates to the lacIq gene. A lacIq gene encodes a transcription repressor. Therefore, applicant submits that the subject matter of claim 121 is within the scope of the presently amended claims of Group II.

In conclusion, applicant has shown that the subject matter of claims 116, 120 and 121 are related to the Group II invention. Therefore, applicant requests that the Examiner include claims 116, 120 and 121 in the Group II claims.

Respectfully submitted,

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VERSIONS WITH MARKING SHOWING CHANGES

Please amend claims 113 and 132 as follows.

113. (amended) A method of making a soluble botulinum toxin comprising:

expressing a botulinum toxin from a prokaryotic expression vector comprising a botulinum toxin nucleotide sequence in a prokaryotic host cell wherein the prokaryotic expression vector includes a weak promoter relative to [a] an unrepressed T7 promoter thereby making a soluble botulinum toxin.

132. (amended) The method of claim 126 wherein the botulinum toxin nucleotide sequence specifically hybridizes under highly stringent conditions to [SEQ ID NO:28] to the nucleotide sequence of SEQ ID NO:27.